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As Hopes Have Flown Before: Toward the Rational Design of Treatments for Alcohol Use Disorder

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I have absolutely no pleasure in the stimulants in which I sometimes so madly indulge. It has not been in the pursuit of pleasure that I periled life and reputation and reason. It has been the desperate attempt to escape from torturing memories, from a sense of insupportable loneliness and a dread of some strange impending doom.

— Edgar Allan Poe

A master of literary Romanticism renowned for his depictions of the macabre, Edgar Allan Poe died tragically at 40 years of age. In the quote above, Poe poignantly describes the compulsive escapist consumption of alcohol (the term “stimulant” conveyed a different meaning in Poe's day). It has been postulated that Poe died because of heavy drinking, causing him to lapse into an alcoholic hepatic encephalopathy, Wernicke–Korsakoff syndrome, or delirium tremens that proved fatal (1). Whatever the cause of his death, it is well known that he struggled with a descent into the maelstrom of alcoholism. During his final months, he attempted to overcome his addiction by joining a temperance movement. Unfortunately, this was one of the only treatment strategies that existed at the time.

The number of treatment options for alcohol use disorder has evolved since Poe's day, reflecting a range of approaches infused with the traditional “moral model,” which views addiction as a personal failing and constitutional weakness, to the biomedical model, which conceptualizes addiction in terms of dysfunction of neural circuits. There are social organizations and informal constructs reminiscent of the temperance movements of the 19th and early 20th centuries (e.g., American Temperance League and Straight Edge). There are also mutual aid recovery organizations (Alcoholics Anonymous), rehabilitation programs, psychosocial and psychological therapies, and pharmacologic treatments. Despite the increase in available options, alcohol remains a major cause of morbidity and mortality.

One of Poe's famous short stories, “The Imp of the Perverse,” describes the human temptation to act against one's best interest. Alcohol use disorder embodies this proclivity. It is among the most common of all addictive disorders and psychiatric conditions. It is estimated that 29.1% of Americans meet the criteria for alcohol use disorder over their lifetime and that this diagnosis is associated with overall disability, psychiatric comorbidity,

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and a higher incidence of other addictive disorders (2). Despite its prevalence, fewer than one in five Americans with alcohol use disorder receive treatment of any kind (2), in large part because of stigma arising from the persistence of the moral model in the modern cultural zeitgeist.

The need for alcohol use disorder treatments is urgent and has fallen far behind that of many nonaddictive psychiatric disorders. As an illustrative example, a recent MicroMedex search for antidepressants listed 34 individual agents, and this number jumps to 63 if formulation variations are taken into account. There are 36 individual antipsychotic agents listed in a similar search and 58 if formulation variations are considered. In contrast, there are five medications listed for alcohol use disorder, only three of which are approved by the U.S. Food and Drug Administration: disulfiram, naltrexone, and acamprosate.

The disparity in the pace of treatment development is similarly stark. The U.S. Food and Drug Administration has approved three new antidepressants since 2011 (vilazodone, vortioxetine, and levomilnacipran) and six antipsychotic agents since 2009 (asenapine, iloperidone, lurasidone, brexpiprazole, cariprazine, and pimavanserin) as well as a novel formulation of aripiprazole. The most recently developed novel pharmacologic agent for alcohol use disorder is acamprosate, approved in 2004. The most recent U.S. Food and Drug Administration approval came in 2006 for Vivitrol (Alkermes, Inc., Waltham, MA), a reformulated depot version of naltrexone. Before the approval of oral naltrexone in 1998, the only approved medication option for 43 years was disulfiram, a treatment that in many ways punishes the poor soul who continues to drink with the specter of future illness and guilt should his or her self-control lapse, not unlike the eerie thumping of “The Tell-Tale Heart.” Even as a medication with a definable molecular mechanism of action, disulfiram acts as a chemical enforcer of the moral model of addiction. Its use is largely predicated upon the assumption that continuing substance use is a conscious and deliberate choice. The fact that trials have failed to show superiority of disulfiram over placebo suggests that moralizing addiction is not sufficient as a treatment approach (3).

Focusing on the underlying neural mechanisms of alcohol dependence may prove to be a more fruitful approach. On a neurobiological level, addiction is the hijacking of neural circuits that ordinarily serve to reinforce evolutionary advantageous behaviors. The functioning of this “reward system” is thought to underlie the positive associations arising from adaptive behaviors, such as parent–offspring contact, sexual intimacy, and the consumption of calorie-dense foods. The dopaminergic mesolimbic pathway is a network of structures that reinforces these adaptive pleasurable activities via dopamine signaling through projections from the ventral tegmental area, located in the midbrain, onto different types of medium spiny neurons in the nucleus accumbens, located in the ventral striatum (4).

The projections from these medium spiny neurons activate two pathways: a striatal reward circuit sometimes referred to as the direct pathway, and a striatocortical circuit, also called the indirect pathway, that is associated with punishment (yes, these are the same direct and indirect pathways also associated with motor control that everyone joyfully memorizes for their Introduction to Neuroscience examinations). Alcohol, like other drugs of abuse, co-opts this system by inducing supraphysiologic levels of dopamine to flood into the nucleus

accumbens, strongly activating the striatal reward pathway and inducing a cascade that ultimately inhibits the striatocortical punishment pathway (4). The simultaneous synergistic activation and inhibition of these respective pathways results in profoundly dysregulated reward perception, emotional salience, and self-control (5).

Here is where things become even more complicated. While we may be used to thinking about alcohol's direct gamma-aminobutyric acidergic effects on the brain—and perhaps even on its impact on the dopaminergic reward pathways—we are less used to thinking of alcohol as acting on the body's endogenous opioid system. However, like heroin or morphine, we now know that alcohol is also a potent stimulant of the endogenous opioid system (6) (Figure 1). Moreover, the dopaminergic and endogenous opioid systems are intimately connected, as inseparable as Poe and his beautiful “Annabel Lee” (down in her sepulcher there by the sea).

Many classes of opioid receptors are present throughout the body, but two are most relevant to our story: the μ opioid receptor and the κ opioid receptor. While exact mechanistic details are still being investigated, broadly speaking, agonism of the μ opioid receptor by its endogenous ligands, β endorphins and enkephalins, is associated with the pleasure of intoxication; on the other hand, the κ opioid receptor, agonized by dynorphin, causes dysphoria and is implicated in the stress response associated with substance withdrawal (4). The nuanced interconnection between these systems explains the nonintuitive finding that manipulation of the endogenous opioid system can be useful for the treatment of addiction to substances other than opioid drugs. For example, the μ opioid receptor antagonist naltrexone has been shown to be effective for the treatment of alcohol use disorder and a host of behavioral addictions (7).

The role of the endogenous opioid system in regulating alcohol dependence is further explored in a fascinating study by Quelch *et al.* (8) in which they describe their findings from a neuroimaging investigation of heavy drinking volunteers meeting DSM-IV criteria for alcohol dependence who were administered the drug nalmefene. The nalmefene molecule has intriguing and potentially useful interactions with the body's endogenous opioid system by possessing mixed actions at various opioid receptor subtypes. Like naltrexone, nalmefene is a μ opioid receptor antagonist; however, it distinguishes itself as a partial agonist at the κ opioid receptor—a system now seen as a promising pharmacological target in the treatment of addiction. The κ opioid-mediated dysphoric effects of substance withdrawal have led researchers to theorize that partial agonism or antagonism of the κ opioid receptor may lead to treatment for a broad array of addictions. Preliminary data are promising, with early evidence demonstrating efficacy of this approach in treating addictions to alcohol, cocaine, nicotine, and cannabis (9).

It is time for our field to do better by our patients who are suffering from alcohol use disorder. We must continue to build upon our rich history of psychosocial interventions by developing more nuanced—and more efficacious—neurobiologically informed treatments. Modulation of the endogenous opioid pathway offers a compelling path forward: naltrexone is already our most effective current treatment, and nalmefene and related agents wait in the wings with the potential for further advances. After centuries of being left weak and weary,

perhaps soon clinicians and patients alike will see the ravages of alcohol abuse, to quote Poe's raven, nevermore.

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Figure 1.

Alcohol influences the dopaminergic mesolimbic pathway by directly increasing dopamine neurotransmission from the ventral tegmental area to the nucleus accumbens, as well as by increasing production of endogenous opioid ligands, thereby modulating outputs to neural circuits that mediate reward and punishment. EtOH, ethanol.